REMARKS

Claim 18 is objected to under 37 C.F.R. 1.75 as being a substantial duplicate of claim 1 if and when claim 1 is allowed. Applicant submits that these claims are not identical in that claim 18 does not include the limitation of "calcium free" as amended which should distinguish over claim 1. Reconsideration is requested.

Claims 1, 9, 14, 17 and 18 now stand rejected under 35 USC 102(b) as being anticipated by Purcell et al. (US 5,945,449).

Claims 1, 9, 14, 17-19 and 21 now stand rejected under 35 U.S.C. 103(a) as being unpatentable over Martis et al (WO 96/01118) in view of Purcell et al.

Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable, if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant therefore has taken the subject matter of claim 10 and prepared that subject matter in newly provided claim 24 for the Examiner's consideration which should therefore be allowable consistent with the Examiner's comments in his report.

The Examiner is referred to Applicant's prior submission dated February 8, 2006 including a review of accepted jurisprudence for anticipation and obviousness, the contents of which are hereby incorporated by reference in its entirety, which will be referred to below.

Claims 1, 9, 14, 17 and 18 now stand rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Purcell et al. (US 5,945,449). The Examiner purports that Purcell et al. explicitly discloses a sterile calcium-free bicarbonate concentrate comprising 86.87 ± 8.6 g/l NaCl, 2.05 ± 0.2 g/l $MgCl_2$, and 39.69 ± 3.9 g/l $NaHCO_3$ and a sterile, diluted solution, wherein 140 ± 14 mM Na, 0.75 ± 0.07 mM Mg, 106.5 ± 10 mM Cl, and 35 mM ± 3.5 HCO_3 are present. However, Applicant has now amended the present claim set to limit the upper limit of bicarbonate to 27.5 mmol/L. This level is not taught in Purcell nor would it be enabled or inherent by the teaching of Purcell nor obvious to do so! A practitioner cannot and would not merely adjust the bicarbonate level by dilution since this effort would also effect the other electrolyte ions to the detriment of any patient <u>including the risk of death</u>. In this regard we attach a second Declaration from Dr. Tobe including test results for a well known respected laboratory affixed as Exhibit B, clearly showing that a simple dilution is not

possible. The second Declaration of Dr. Tobe is hereby incorporated by reference in its entirety into this response as if its entire contents were presented herein.

Referring to US Patent 5,945,449 to Purcell there is taught a sterile solution containing 35.0 ± 3.5 mmol/L of bicarbonate. At no time does Purcell teach a bicarbonate level of less than 31.5 mmol/L. However the present invention rests in the discovery and the implementation thereof that addresses and seeks to maintain normal bicarbonate levels of approximately 25 mmol/L. When an anticoagulant such as lactate or citrate is added to the dialysis solution the liver will convert the weak acid to bicarbonate. The present dialysis solution provides for an allowance of this fact wherein the original NORMOCARB® 35 did not. By providing a sterile dialysis solution having a bicarbonate level of from 5 to 27.5 mmol/L an accommodation is made for the conversion in the liver of the weak acid to bicarbonate which is not contemplated in Purcell. Therefore Purcell cannot be considered as enabling. The Examiner has incorrectly alleged that it is inherent in Purcell to dilute same to arrive at the present invention. There is no motivation in Purcell to do so. As found in the current disclosure and particularly the summary of the invention the use of a low bicarbonate dialysis solution of the invention takes into account any bicarbonate derived from the weak acid if used as an anticoagulant, for example citrate. Thus metabolic complications are effectively minimized. The benefit of such a low concentration of bicarbonate of for example 25 mmol/L, is if the patient's bicarbonate level drops below this level, bicarbonate diffuses from the dialysate across the semi-permiable membrane to the patient correcting the problem. If there is an excess of bicarbonate in the blood (metabolic alkalosis), then bicarbonate will diffuse out into the dialysate and be removed from the blood returning the patient toward the normal level. The present invention includes a sterile calcium-free low bicarbonate concentrate containing magnesium, sodium chloride and a low concentration of bicarbonate that can be used in a number of novel applications, for example continuous renal replacement therapies, such as continuous dialysis and hemofiltration. The Examiner is referred to the disclosure for more particulars with respect to the advantages of the present invention.

At no time however did Purcell contemplate providing a low bicarbonate concentrate for the purposes described above to accommodate for the conversion of the weak acid to bicarbonate in the liver. Therefore Purcell is not enabling with respect to the present invention as defined in the amended claim set. Further there is no motivation in Purcell to do so since Purcell did not even appreciate the problem which Applicant has addressed. In fact none of the other references and inventors appreciated this problem.

The inventor of the present application is Dr. Sheldon Tobe, M.D., who is an Associate Professor of Medicine at the University of Toronto and currently is the Staff Nephrologist at the Sunnybrook Health Sciences Centre in Toronto, Ontario. Dr. Tobe has reviewed Purcell and the other prior art cited within the Examiner's Report and we attach hereto his further comments in the form of a second Declaration which again is hereby incorporated by reference in its entirety in this response as if the comments were made directly herein. Although the bicarbonate solution of Purcell is mixed in a ratio of 80ml ± 1ml of concentrate to 1L of sterile physiologically acceptable diluent, such as water, the net result of the solution is a bicarbonate of 35.0 ± 3.5 mmol/L or a 10% leeway in either direction. In Dr. Tobe's opinion the instructions are pretty specific and the concentrate should be diluted exactly as described without going more than 10% in either direction. In fact going more than 10% in either direction may become fatal if used in a dialysis regimen. This is because all of the other electrolytes besides bicarbonate would be diluted as well and the dialysis solution namely NORMOCARB® is designed for exactly the specified dilution as discussed above namely 80ml to 1L. If the original NORMOCARB® 35 were diluted, in an attempt to create a bicarbonate of 25 mmol/L, this would result at a concentration of 71.43% of the original NORMOCARB® 35 thereby reducing the sodium from 140 to 100 and the chloride from 106.5 to 76.1. This is further demonstrated in Exhibit B of Dr. Tobe's second declaration clearly proving that merely diluting Purcell will not arrive at the present invention. The report is self explanatory. In Dr. Tobe's expert opinion, as restated here, the resulting solution alleged by the Examiner as being inherent from Purcell and an obvious variation, would in fact not be safe for use and might likely result quickly in the death of a patient. Diluting the overall solution without adjusting each component for the specific use, namely the condition being treated, would be totally unacceptable from a medical perspective. The Examiner is entirely incorrect, respectfully, that merely adding a bit of fluid to the concentrate to adjust and obtain a low bicarbonate would be easily accomplished. This ignores that the resulting sodium of 100 would be entirely unacceptable. Dr. Tobe also says that it's not inherent in the Purcell concentrate to so dilute that concentrate to result in a bicarbonate of 25 mmol/l. He has even stated in his first declaration that in doing so a physician may be faced with a malpractice suit. Further Dr. Tobe has stated that he would not approve the use of NORMOCARB® 35 for this application. Dr. Tobe further states that any attempt to dilute the bicarbonate to a level of 5 mmol/l results in a ludicrous result of sodium of approximately 20 which would frankly be toxic and hemolize the red cells on contact. Respectfully the Examiner has clearly misread the original Purcell patent which clearly cannot be considered as enabling in view of Dr. Tobe's opinions, and the present amended claim set.

The claims have now been amended to identify over Purcell in the broadest sense to be limited to the range of 5 to 27.5 mmol/L of bicarbonate which is not contemplated in Purcell since Purcell only teaches a bicarbonate lower limit of 31.5 mmol/L. Dr. Tobe also states in his second declaration that preparing a solution to correct any diluted NORMOCARB® 35 to result in NORMOCARB® 25 was more difficult than originally developing NORMOCARB® 35.

It is therefore requested that the Examiner reconsider his rejection of the claims on the basis of Purcell since the ion concentration of the present invention is different and clearly for a different purpose namely to compensate for the conversion of weak acids to bicarbonate in the liver. Purcell did not make this compensation part of his invention and clearly it is not evident from the teachings of Purcell to do so. Although the Purcell composition is suitable for hemodialysis and peritoneal dialysis the properties of the actual concentrate and dialysis solution are quite different. Therefore all of Applicants claimed features are absent from Purcell and the claims cannot be anticipated especially in view of the present amendments, as is a requirement specified in the prior mentioned jurisprudence previously précised. According to accepted jurisprudence for a reference to anticipate it must be enabling and include each and every limitation of the claims. This is not the case in view of the present amendments and the above-mentioned arguments and full reconsideration is requested and withdrawl of the Examiner's rejection is also further appreciated.

Out of an abundance of caution it is surmised the Examiner might also cite Purcell as a reference to allegedly render obvious the claims of the present application. For the same reasoning described above this cannot be the case since there is no motivation within Purcell to one skilled in the art to arrive at Applicant's present amended claim set. According to the accepted jurisprudence of Graham v. John Deere, Applicant has set out the differences between the present claim set as amended and the prior art and has established that the claims result in more than anything that might have been contemplated by Purcell. This is further supported by the evidence in Exhibit B filed with Dr. Tobe's second declaration. Full reconsideration is respectfully requested.

Claims 1, 9, 14, 17-19 and 21 now stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Martis et al. (WO 96/01118) in view of Purcell et al. The Examiner alleges that Martis et al. discloses a peritoneal dialysis solution. Applicant agrees. But Martis does not teach a dialysis solution for continuous renal replacement therapy which is an all together

different process. The claims are now limited to such a process. Further the Examiner is advised that Martis in fact teaches an effective bicarbonate level of over 30 mmol/L since the weak acid incorporated in Martis will be converted by the liver to bicarbonate at a one to one conversion rate. Therefore Martis in fact includes effective bicarbonate levels of 30 to 50 mmol/l which clearly is well above the effective upper limit of 27.5 mmol/L provided in Applicant's amended claim set. Please refer to Dr. Tobe's comments in that regard.

Referring now to Martis (WO 96/01118) hereinafter referred to as Martis, the Examiner alleges that the bicarbonate level is in the range of 20 to 30 mEq/L without taking notice that a weak acid is provided in the range of 10 to 20 mEq/L which as discussed above would be converted to bicarbonate in the liver. Martis discusses a peritoneal dialysis solution only and provides for the weak acid which might be lactate, pyruvate, citrate, isocitrate, etc. Referring to Martis there is taught the step of administering to the patient of a weak acid present in the solution in an amount that offsets the daily hydrogen production of approximately 1 mEq/kg per day. This is an admission of Martis in the mind of Dr. Tobe that the purpose of the weak acid is to be metabolized into something that offsets daily hydrogen production namely it is metabolized to bicarbonate. This teaching of Martis includes a solution having 20 to 30 mmol/L of bicarbonate, but the Examiner fails to recognize that the 10 to 20 mmol/L of the weak acid gets converted directly to bicarbonate, yielding a range of effective bicarbonate from 30 to 50 mmol/L which is well beyond the range of 5 to 27.5 mmol/L in the present claims. Martis does not contemplate a total bicarbonate equivalent level of below 27.5 mmol/L since the minimum level of bicarbonate and bicarbonate equivalents as taught in Martis is no less than 30 mmol/L and above.

The teachings of Martis are not relevant to the present claim set. One must conclude that Martis is not enabling in this regard and would not provide sufficient motivation to one skilled in the art to arrive at Applicant's invention.

NORMOCARB® 25 was designed for patients who have reached normal levels of bicarbonate. The principle of maintaining a bicarbonate level around the normal physiologic level of 25 is an important principle. If the body's bicarbonate level rises above 25, bicarbonate will diffuse into dialysate. If the body's bicarbonate drifts below 25 bicarbonate will be added to it from the dialysate. This principle also works for the other electrolyte components available in NORMOCARB® 25.

Referring now to the Examiner's allegations with respect to Martis in view of Purcell, what would Martis in fact glean from Purcell. The motivation is lacking in Purcell to provide a dialysis solution in the range of 5 to 27.5 mmol/L for the reasons set out above. This motivation is also lacking in Martis. How then, could the Examiner's alleged combination result in an effective in vivo bicarbonate concentration of 5 to 27.5 mmol/L, again taking into consideration that the weak acid converts in the liver to bicarbonate equivalents. The Examiner freely admits that the composition make-up of Purcell is different and he relies on the knowledge of one skilled in the art to provide a sterile dialysis solution within the range of Applicant's limitations. However Applicant has submitted a second Declaration in this regard to prove that this is incorrect. In any event, the Examiner's alleged combination of Martis in view of Purcell would still fall significantly short of Applicant's amended claims and therefore the claims are most assuredly, as amended, novel and inventive. Full reconsideration is therefore requested, especially in view of Dr. Tobe's further evidence.

The traditional test enunciated in Graham vs. John Deere Company 383 U.S. 1, 148 U.S.P.Q. 459 1966, for Section 103 nonobviousness requires the fact finder to make several determinations. The test provides that the scope and content of the prior art namely Martis in view of Purcell be determined, the differences between the prior art namely Martis in view of Purcell and the claims at issue be ascertained, as setout in the two declarations of Dr. Tobe, and the level of ordinary skill in the pertinent art be resolved. Thus, the patentability of the claims at hand stems from the fact that the specific combination of the claimed elements present in Applicant's claims as amended was not disclosed in Martis or Purcell or any combinations thereof and the additional allegation that the specific combination of claimed elements was nonobvious to one of ordinary skill in the art as argued herein and supported by Dr. Tobe's two declarations.

Clearly, the prior art does not suggest or provide any reason or motivation to make such a modification as purported by the Examiner. With reference to In Re: Regal, 526 F. 2d 1399, 1403 n. 6, 188 USPQ 136, 139 n. 6 (CCPA 1975).

> "There must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references".

In Re: Geiger, 815 F. 2d 686, 688, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987) (obviousness can not be established by combining pieces of prior art absence some "teachings, suggestion, or

incentive supporting the combination"): In Re: Cho. 813 F. 2d 378, 382, 1 USPQ 2d 1662, 1664 (Fed. Cir. 1987)("discussing the Board's holding that the artisan would have been motivated to combine the references").

Therefore, it Applicant's view there is no evidence of motivation in the prior art, either within the references themselves, or knowledge generally available to one of ordinary skill in the art, to make the purported changes suggested by the Examiner to arrive at the claimed subject matter.

Respectfully, the Examiner is creating a 20/20 hindsight reconstruction using Applicant's invention as a blue print to allegedly find elements of Applicant's combination in the prior art. This is not permissible as set out below.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

> "Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. **It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious**(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

In view of applicant's submissions full reconsideration of all allegations of anticipation and obviousness is respectfully requested. It is submitted that all issues have been addressed herein by amendment and rebuttal including expert evidence and a Notice of Allowance is appreciated.

Lastly the Examiner has reminded Applicant about his duty to disclose "all information known to be material to patentability" in this application with respect to NORMOCARB® product information. The Examiner is advised that NORMOCARB® owned by the Assignee was marketed originally by the Assignee in 2001 consistent with the teachings of Purcell and was based on those teachings. In support Applicant includes the Register pages for Canada and the United States indicating a Declaration of Use being filed in 2001. Applicant had previously advised the Examiner of this fact. NORMOCARB® 25 was first approved to be marketed in about 2005 using the NORMOCARB® trademark. Applicant encloses the most

current product monograph and approval letter from the FDA in this regard for the Examiner's information.

If any questions arise, the Examiner is respectfully requested to contact Neil Hughes at (905) 771-6414 at the Examiner's convenience.

Respectfully submitted,

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Agent for the Applicant

NHH/lvp
Encls. Second Declaration of Dr. Tobe
CA and US Register pages for NORMOCARB®
FDA Approval Letter for NORMOCARB® 25
Product Monograph for NORMOCARB® 35 & NORMOCARB® 25